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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/HU2004/000077	16.07.2004	16.07.2003

International Patent Classification (IPC) or both national classification and IPC
A61K31/42, C07D231/12

Applicant
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1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/HU2004/000077

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3-5,8-21
	No:	Claims	1,2,6,7
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-21
Industrial applicability (IA)	Yes:	Claims	1-18
	No:	Claims	19-21?

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

The present application relates to *N*-hydroxy-4-(3-phenyl-5-methyl-isoxazole-4-yl)-benzenesulfonamide and its solvates, as well as to preparation and therapeutical uses thereof, namely for the treatment of osteoarthritis and rheumatoid arthritis and surgical and primary dysmenorrheal pains.

Reference is made to the following documents:

D1: JOSH J. YUAN ET AL.: "Disposition of a specific cyclooxygenase-2 inhibitor, valdecoxib, in human" DRUG METABOLISM AND DISPOSITION, vol. 30, no. 9, 2002, pages 1013-1021, XP002311618

D2: JOHN J. TALLEY ET AL.: "4-[5-Methyl-3-phenylisoxazol-4-yl]-benzen esulfonamide, Valdecoxib: A potent and selective inhibitor of COX-2" J.MED.CHEM., vol. 43, 2000, pages 775-777, XP002311619

D3: HERBERT T. NAGASAWA ET AL.: "Carbethoxylating agents as inhibitors of aldehyde dehydrogenase" J.MED.CHEM., vol. 38, 1995, pages 1872-1876, XP002311620

D4: MAURICE L. MOORE ET AL.: "Substituted sulfanilamides. III. N4-Acyl-N1-hydroxy derivatives" J.AM.CHEM.SOC., vol. 62, 1940, pages 2097-2099, XP002311621

Re Item V

Novelty (Art. 33(2) PCT)

Document **D1** states (cf. abstract, and Fig. 5) that the primary oxidative metabolic pathway of valdecoxib involves hydroxylation at either the methyl group to form M1 or *N*-hydroxylation at the sulfonamide moiety to form M2 (*N*-hydroxy-4-(3-phenyl-5-methyl-isoxazole-4-yl)-benzenesulfonamide). Both metabolites were identified: pg. 1018, col. 1, par. 2 and pg. 1018, col. 2, par. 2. It is clear that in the conditions of electronic ionization, the compound M2 is not in a solvate form, whereas it may be assumed, that in an aqueous solution (e.g. urine), it is in its hydrate form. The subject-matter of claims 1, 2, 6, and 7 may therefore not be regarded as novel.

Inventive Step (Art. 33(3) PCT)

D2 is considered to be the closest state of the art. This document shows (cf. pg. 776, col. 2, par. 2-3) that valdecoxib and its metabolite resulting from oxidation at the methyl group

are selective and potent inhibitors of COX-2. The presently claimed compounds, compositions, uses and methods differ from **D2** in that the substance involved is **another primary metabolite of valdecoxib obtained by oxidation**. The problem to be solved by the application may thus be regarded as providing **alternative** compounds, compositions, uses, and methods to those disclosed in **D2**.

In view of the metabolic route disclosed in **D1** (cf. Fig. 5), wherein *N*-hydroxy-4-(3-phenyl-5-methyl-isoxazole-4-yl)-benzenesulfonamide (M2) is one of the three primary metabolites obtained by oxidation of valdecoxib (the compound of **D2** is another one), it would be obvious for the skilled person in the search of alternative compounds to test *N*-hydroxy-4-(3-phenyl-5-methyl-isoxazole-4-yl)-benzenesulfonamide in the expectation of achieving comparable results. Hence, the subject-matter of claims 1-7 and 14-21 may not be regarded as inventive.

Claims 8-11 relate to the preparation of the compound (I) or its solvates by chlorosulfonylation of an aromatic ring followed by nucleophilic substitution of the chlorine by hydroxylamine. However, this appears to be one of the usual methods of preparation of aromatic *N*-hydroxy sulfanilamides, as can be seen e.g. in **D3** (pg. 1875, col. 2, last par.) or **D4** (pg. 2098, col. 1, par. 2-3). Thus, the subject-matter of claims 8-11 does neither involve an inventive step.

With regard to claims 12 and 13, heating or vacuum-heating are the most common procedures in the art for the obtention of solvate-free compounds. Therefore, the subject-matter of claims 12 and 13 may not be regarded as inventive.

Industrial applicability (Art. 33(4) PCT)

Is acknowledged for claims 1-18.

For the assessment of the present claims 19-21 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for fist use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Claims 8 and 11 are not clear (Article 6 PCT) in that they do not state if a) and b) are two alternatives or consecutive steps.

Claims 14, 15, and 19-21 do not fulfil the requirements of Article 6 PCT in that it is not clear to what extent the feature "based on anti-inflammatory and analgesic pharmacological model experiments" limits the claimed uses or methods. Said feature renders the scope of the claims obscure.